Clinical review

Regular review

Peripheral neuropathy

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Peripheral neuropathy is common, often distressing, and sometimes disabling or even fatal. The population prevalence is about 2400 per 100 000 (2.4%), rising with age to 8000 per 100 000 (8%).[1] In Europe the commonest cause is diabetes mellitus, which can produce painful neuropathy, disabling foot ulcers, and death from autonomic neuropathy. Leprosy is still prevalent in Africa, India, and South East Asia. This review explains how general practitioners can approach the first level of diagnosis and warn patients about what lies ahead after referral to a specialist.

Summary points

- Peripheral neuropathy can be into divided into acute and chronic forms, symmetrical polyneuropathy, and multiple mononeuropathy
- Acute neuropathies are diagnostic emergencies
- Neuropathy due to diabetes mellitus and alcohol misuse can be diagnosed in primary care
- Neurophysiological tests distinguish axonal from demyelinating neuropathies
- Demyelinating neuropathies are commonly inflammatory and treatable
- Axonal neuropathies have multiple causes
- Generic management includes foot care, ankle supports, and treatment of neuropathic pain

Methods

I searched Medline from January 1991 until September 2001 using the terms "peripheral neuropathy" and "guideline." The search yielded 11 references, including useful guidelines for the diagnosis and management of diabetic peripheral neuropathy,[2] but no guidelines on the diagnosis and management of generic peripheral neuropathy. This article offers a personal approach to the management of generalised peripheral neuropathy from the perspective of a neurologist with a special interest in the topic. The recommendations also take account of reviews published by authorities in peripheral neuropathy (see educational resources) and a recent audit of a Dutch departmental guideline that showed the value of investigating common causes before doing electrophysiological tests.[3]

Diagnosis

Patients with peripheral neuropathy may present with altered sensation, pain, weakness, or autonomic symptoms. The clinical features vary widely and may resemble myelopathy, radiculopathy, muscle disease, or even hyperventilation. Identifying a neuropathy in patients with coexistent problems can therefore be difficult. The symptoms usually begin in the toes before the fingers and spread proximally.

The classic picture of advanced polyneuropathy with distal wasting and weakness, absent tendon reflexes, and glove and stocking sensory loss should be easy to recognise. The clinical features allow acute symmetrical peripheral neuropathy, chronic symmetrical peripheral neuropathy, and multiple mononeuropathy to be distinguished, each with a different differential diagnosis.

Acute symmetrical peripheral neuropathy

Acute symmetrical peripheral neuropathy is rare but important because the commonest cause is Guillain-Barré syndrome, which can be fatal. The table gives other causes. Common early symptoms are distal paraesthesiae and proximal or distal weakness occurring one to two weeks after a respiratory or gastrointestinal infection. Traditionally, the reflexes are absent, but their retention during the first hours of the illness has led many patients to be dismissed as "hysterical." Once a patient loses the ability to walk and develops facial and bulbar weakness the diagnosis becomes obvious. The rapid progression of sensory or motor deficit requires emergency investigation. Patients usually have to be admitted to hospital because of the danger of respiratory failure. Early treatment should stop the pathological process before axonal dysfunction becomes irreversible.

Guillain-Barré syndrome is usually due to acute inflammatory demyelinating polyradiculoneuropathy caused by an autoimmune response directed against the Schwann cells or myelin. Some cases are due to acute axonal neuropathy, in which glycolipid in the axolemma is targeted. In both forms, treatment with intravenous

immunoglobulin hastens recovery and reduces the long term disability and is more convenient than plasma exchange.[4] A recent trial suggests that combination treatment with steroids is more effective than intravenous immunoglobulin alone, but the full results are awaited.[5]

Multiple mononeuropathy

Acute multiple mononeuropathy is also a neurological emergency because the commonest cause is vasculitis (box 1). Prompt treatment with steroids may prevent further irreversible nerve damage. If multiple mononeuropathy develops in a patient with an established connective tissue disorder (such as rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, or Churg-Strauss syndrome) it is reasonable to conclude that vasculitis is the cause. Steroids are the main treatment, with cyclophosphamide being added depending on the severity and general medical condition.

Sometimes peripheral neuropathy is the presenting or sole feature of vasculitis. In this case, vasculitis can be diagnosed only by nerve biopsy.[6,7] In addition, recent biopsy studies indicate that diabetic amyotrophy is due to microvasculitis in the lumbosacral plexus. It presents acutely with pain, weakness, and then wasting in one or both quadriceps muscles.[6–8]

Chronic symmetrical peripheral neuropathy

Most peripheral neuropathies are chronic and usually develop over several months. Diagnosis of the underlying cause may require three stages of investigation. Any history of a general medical disorder could be relevant. Patients should always be asked about alcohol consumption, toxin exposure (insecticides, solvents), and drugs. They should also have a full examination, including breasts and genitalia, to exclude underlying carcinoma.

The commonest causes of neuropathy can be identified from the history, examination, and simple stage 1 investigations (box 2). Sometimes the neuropathy is predominantly sensory and subacute with ataxia that is worse in the dark because of loss of large fibre function and postural sensation. This pattern is produced by some drugs (such as cisplatin), an underlying neoplasm, Sjögren's syndrome, or idiopathic sensory neuronopathy. If other members of the family have similar symptoms, pes cavus, or claw toes, the patient may have hereditary motor and sensory neuropathy or Charcot-Marie-Tooth disease, which is usually autosomal dominant. Difficulty with walking in childhood also suggests a hereditary neuropathy. If patients have a clear cause for their neuropathy and a typical clinical picture, treatment—for instance, of diabetes mellitus or alcohol misuse—can be started without further investigation.

Causes of acute severe generalised peripheral neuropathy

Cause	Predominantly motor	Mixed	Predominantly sensory
Guillain-Barré syndrome	+	+	—
Vasculitis	—	+	—
Diabetes mellitus	—	+	+
Drugs*	—	+	+
Porphyria	+	—	—
Diphtheria	—	+	—
Paraneoplastic neuropathy	—	+	+
Acute idiopathic sensory neuronopathy	—	—	+
Critical illness	+	+	—

*For example, nitrofurantoin, vincristine, cisplatin, and reverse transcriptase inhibitors.

Box 1: Causes of multiple mononeuropathy

Vasculitis
Primary systemic vasculitis:
- Polyarteritis nodosa
- Churg-Strauss syndrome (vasculitis with blood eosinophilia and asthma)

Systemic vasculitis associated with connective tissue diseases:
- Rheumatoid arthritis
- Sjögren's syndrome

Vasculitis confined to peripheral nerves

Other causes
Sarcoidosis
Lymphoma
Carcinoma
Amyloid

Multiple compression palsies
Associated with metabolic or toxic neuropathy
Hereditary neuropathy with liability to pressure palsies

Second stage investigations

If the cause of the neuropathy is not clear from the stage 1 investigations or is atypical, the patient should be referred to a neurologist. The most important stage 2 investigation is neurophysiological testing (figure). About 80% of symmetrical peripheral neuropathies are axonal and are due to gradual dying back of the axons. In the remaining 20% (demyelinating neuropathies) most of the damage is to the myelin, although axonal degeneration often occurs as the disease advances. The other second stage investigations (box 2) are simple outpatient tests for the commonest causes of peripheral neuropathy.

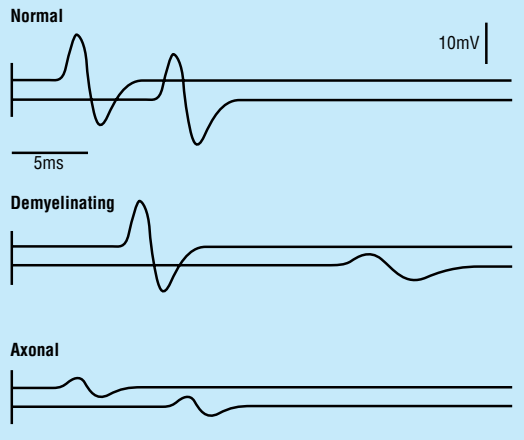
Third stage investigations

The choice of third stage investigation will depend on whether neurophysiological testing has shown the neuropathy to be demyelinating or axonal.

Box 2: Stage 1 and 2 investigations of peripheral neuropathy

Stage 1
Urine—Glucose, protein
Haematology—Full blood count, erythrocyte sedimentation rate, vitamin B-12, folate
Biochemistry—Fasting blood glucose concentration, renal function, liver function, thyroid stimulating hormone

Stage 2
Neurophysiological tests—Assessment of distal and proximal nerve stimulation
Biochemistry—Serum protein electrophoresis, serum angiotensin converting enzyme
Immunology—Antinuclear factor, antiextractable nuclear antigen antibodies (anti-Ro, anti-La), antineutrophil cytoplasmic antigen antibodies
Other—Chest radiography



Muscle action potentials after distal and proximal stimulation of a nerve to a muscle such as abductor pollicis brevis. The upper trace of each pair is the record after distal stimulation. In the normal nerve the distal motor latency is short and nerve conduction velocity rapid (>50m/sec). In demyelinating neuropathy the distal motor latency is prolonged and nerve conduction velocity slowed to less than 80% of normal. In axonal neuropathy the action potential is reduced, but the distal motor latency and nerve conduction velocity are unaffected. Multifocal abnormalities with normal conduction velocity suggest multiple mononeuropathy

Demyelinating neuropathy

The causes of demyelinating neuropathy are limited (box 3). If the slowing of nerve conduction affects all nerves roughly equally the diagnosis is likely to be the demyelinating form of Charcot-Marie-Tooth disease (type 1). Seventy per cent of such patients have a duplication of the gene for a 22 kDa peripheral nerve myelin protein on chromosome 17. The duplication causes overexpression of the protein. The clinical picture ranges from classic pes cavus with inverted champagne bottle legs to scarcely detectable clawing of the toes. Different mutations of the same protein and of other myelin proteins cause a similar clinical picture. Genetic counselling and prenatal diagnosis can be offered.

About 10% of patients with a demyelinating neuropathy have a serum paraprotein. Although occasionally associated with a solitary plasmacytoma, the paraprotein is usually benign. The commonest syndrome is a slowly progressive predominantly sensory neuropathy with an IgMκ paraprotein. The paraprotein is an autoantibody directed against the carbohydrate epitopes on myelin associated glycoprotein. The antibody is directly responsible for the neuropathy.

Box 3: Causes of chronic demyelinating neuropathy

- Charcot-Marie-Tooth disease type 1
- Other forms of Charcot-Marie-Tooth disease
- Hereditary liability to pressure palsies
- Other genetic causes—for example, Refsum's disease, metachromatic leucodystrophy
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Multifocal motor neuropathy
- Paraproteinaemic demyelinating neuropathy:
  - Associated with monoclonal gammopathy of undetermined significance
  - Associated with solitary myeloma

Chronic inflammatory demyelinating polyradiculoneuropathy is the commonest form of acquired demyelinating neuropathy and affects about 2 per 100 000 of the population.[9] The disease is usually predominantly motor, and patients show a proximal as well as distal pattern of weakness; the condition may be relapsing and remitting. Protein concentrations in the cerebrospinal fluid are almost always increased. Chronic inflammatory demyelinating polyradiculoneuropathy is diagnosed by exclusion of the other causes listed in box 3 and from neurophysiological testing, which shows multifocal abnormalities with partial conduction block. This causes the compound muscle action potential following proximal stimulation to be smaller than that following distal stimulation (see figure). It is thought to be an autoimmune disease because of the inflammation in the nerves and response to immunotherapy. There is no diagnostic immunological test, but antibodies to the 28 kDa P0 myelin glycoprotein were identified in about a quarter of cases in a recent series and have been shown to induce experimental demyelination.[10]

Chronic axonal neuropathy

Axonal polyneuropathy can be sensory or sensory and motor. It has many causes, which will often be suggested by the history or examination. The third stage investigations (box 4) should show the less common general medical disorders and identify cases of diabetes mellitus that were not detected by the fasting blood glucose test.[11] Nerve biopsy should usually be done only on patients with distressing neuropathy in whom it might lead to useful treatment.[12] In an audit of 50 cases the biopsy confirmed the diagnosis in 70%, affected management in 60%, and caused persistent pain in 33% of patients.[12] Biopsy should be done in a specialist centre and only when the diagnosis cannot be made in any other way. Specimens are usually taken from the sural nerve under local anaesthetic. Vasculitis is the diagnosis most likely to be found.

After exhaustive investigation no clear cause is found in about 25% of patients. Such chronic idiopathic axonal neuropathy usually occurs in elderly people and is often indolent, predominantly sensory, and length dependent. Patients can be reassured that, although their condition may progress, it will usually do so only slowly and is unlikely to become seriously disabling.[13]

Loss of pain and temperature sensation and spontaneous neuropathic pain, described as burning or pricking, can be prominent symptoms of axonal neuropathy. They are due to degeneration of thinly myelinated and unmyelinated nerve fibres. Occasionally small fibre neuropathy occurs without the thicker myelinated nerve fibres being affected and the nerve conduction test results remain normal. The diagnosis in such cases usually relies on the clinical symptoms and signs alone. Proof of the diagnosis would require skin biopsy or enumeration of unmyelinated nerve fibres in electron micrographs of a nerve biopsy specimen.

Chronic axonal neuropathy occurs in patients with many multisystem hereditary disorders. The diagnosis of these conditions is usually suggested by the other neurological and systemic features. Isolated cases of hereditary neuropathy such as the axonal form of Charcot-Marie-Tooth disease (type 2) can, however, be

difficult to diagnose.[14 15] In this disease the symptoms usually begin in childhood and are associated with pes cavus and claw toes but may not come to attention until middle or old age. The family history may not be evident without examination of the apparently unaffected relatives. The condition is clinically and genetically heterogeneous, and several gene loci are involved. Molecular genetic tests are available for only a tiny proportion of patients.

Treatment

Any underlying medical cause of peripheral neuropathy, such as diabetes mellitus or vitamin B-12 deficiency, should be treated. Chronic inflammatory demyelinating polyradiculoneuropathy is important to recognise because it is treatable. Corticosteroids are usually used initially as they are the cheapest treatment, but the condition also responds to intravenous immunoglobulin, plasma exchange, and some immunosuppressant drugs.[9] The uncommon variant, multifocal motor neuropathy, responds to intravenous immunoglobulin and possibly immunosuppressant drugs but not to corticosteroids or plasma exchange.[16] Unfortunately, no specific treatment is available for chronic idiopathic axonal polyneuropathy.

Management

Preventive and palliative treatments include foot care, weight reduction, and sensible shoes, boots, or ankle-foot orthoses. Patients with severe leg weakness may need sticks, crutches, or a walking frame. Physiotherapists are best placed to prescribe these aids, which may need to be adapted to take account of weakness of the hands. Simple wrist splints can help weak wrist extension. More complex splints for weak fingers and hands are usually cumbersome and rarely used. Disabled patients require help from a multidisciplinary team including an occupational therapist, who can advise on special utensils and home adaptations. Some drugs help. Sildenafil may correct erectile impotence. In the United Kingdom, the NHS will pay if the neuropathy is due to diabetes mellitus.

Patients with neuropathy may experience pain, which can be severe and out of proportion to any sensory or motor deficit. Painful neuropathy is difficult to treat. The most useful drugs are anticonvulsants, especially gabapentin and carbamazepine, and tricyclic antidepressants, especially amitriptyline. The opioid-like analgesic tramadol has also been shown to be useful in randomised controlled trials.[17]

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Box 4: Stage 3 investigation of peripheral neuropathy

Urine—Bence-Jones protein

Biochemistry—Oral glucose tolerance test

Cerebrospinal fluid—Cells, protein, immunoglobulin oligoclonal bands

Immunology—Anti-HIV antibodies, antineuronal antibodies (Hu, Yo), antigliadin antibodies, serum angiotensin converting enzyme, antiganglioside antibodies, antimyelin associated glycoprotein antibodies

Tests for Sjögren's syndrome—Salivary flow rate, Schirmer's test, Rose Bengal test, labial gland biopsy

Search for carcinoma, lymphoma, or solitary myeloma—Skeletal survey, pelvic ultrasonography, abdominal and chest computed tomography, mammography, or positron emission tomography

Molecular genetic tests—Peripheral nerve myelin protein 22 gene duplication (the commonest cause of Charcot-Marie-Tooth disease type 1) or deletion (hereditary neuropathy with liability to pressure palsies), connexin 32 mutation (X linked Charcot-Marie-Tooth disease), PO gene mutation (another cause of Charcot-Marie-Tooth disease type 1), etc

Additional educational resources

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Patient information

Guillain-Barré Syndrome Support Group (www.gbs.org.uk)
Information and support for people with Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, and related conditions

Peripheral Neuropathy Trust (www.neuropathy-trust.org)
Information about all forms of neuropathy, especially chronic idiopathic axonal neuropathy

CMT United Kingdom (www.cmt.org.uk)
A site maintained by the UK Charcot-Marie-Tooth disease patient support group